Mechanisms of human induced neuronal cell reprogramming

Grant Award Details

Mechanisms of human induced neuronal cell reprogramming

Grant Type: Basic Biology V

Grant Number: RB5-07466

Project Objective: The overall hypothesis of this proposal is that a detailed molecular comparison of the reprogramming process of neonatal (permissive) and adult (refractory) fibroblasts will reveal the barriers or lack of co-activators in adult fibroblast reprogramming and provide a rational basis to improve the process. Specifically, they plan to assess transcription factor access to the chromatin to identify important target sites that are inaccessible in adult cells and try to “unmask” those sites. They further propose to determine critical downstream transcription factors mediating the reprogramming process and if required supplement them in adult cells. Finally, they propose to understand the mechanism of the donor program silencing to further facilitate the induction of the neuronal fate.

Investigator:

Name:	Marius Wernig
Institution:	Stanford University
Type:	PI

Human Stem Cell Use: Directly Reprogrammed Cell

Award Value: $1,178,370

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Mechanisms of human induced neuronal cell reprogramming

Public Abstract: We and other groups have recently shown that it is possible to convert skin cells from foreskin of newborns into nerve cells that closely resemble nerve cells of the brain in terms of both shape and functional properties. If it were possible to also reprogram human adult skin cells into similarly functional nerve cells, we would be able to generate functional nerve cells from patients that are suffering from a variety of brain diseases. These cells could be used to study the processes underlying these diseases. Furthermore, new skin-derived nerve cells could be used for novel transplantation-based therapies for neurodegenerative diseases such as Parkinson's disease. It is also conceivable that brain cells other than nerve cells could be converted in the living brain into specific nerve cells that are lost due to the disease process.
However, all these potential translational applications rely on our ability to generate functional nerve cells not only from newborns but also from adult skin cells. Unfortunately, all efforts to convert human adult fibroblasts into mature functional nerve cells have failed thus far. We reason that there must be molecular differences between newborn and adult cells that are responsible for the lack of reprogramming. In this proposal we suggest to identify these molecular blockers of nerve cell reprogramming from adult skin cells, which would enable us to devise methods to overcome these blockers.

Statement of Benefit to California: The goal of our proposal is to enable the reprogramming of adult human skin cells into fully functional and mature nerve cells. If successful, these reprogrammed nerve cells could be used for a variety of clinical applications. First, such cells could be derived from patients suffering from a variety of neurodegenerative diseases such as Parkinson's and Alzheimer's disease but also neurodevelopmental diseases such as Autism, Schizophrenia, or bipolar disease. Such nerve cells could then be used to capture processes that underlie those diseases which would enable us to test ways to block these disease processes such as the testing of small molecule drugs. Another potential use of these cells would be cell transplantation. In particular neurodegenerative diseases (i.e. diseases where neurons are lost) would be good candidate diseases for such an approach as one could attempt to generate nerve cells in the dish and use them to replace those nerve cells that are lost in the brain. Finally, this nerve cell reprogramming method could be used directly in the brain without any cell transplantation. It is conceivable that the delivery of just a handful of reprogramming factors directly into the brain can convert non-nerve cells into new nerve cells that again could take over function of previously lost cells. Our proposal is an important first step towards the realization of these applications that aim to improve the life of people that suffer from incurable disease.